

**REMARKS**

**Claim Amendments**

Claims 1-67 are pending. By the present amendment, claims 1, 5, 10-13 and 16-20 have been amended and claims 21-22, 36-45, 53-59 and 65-67 have been canceled. Claims 11, 24-35, 46-52 and 60-64 are withdrawn at the present time as being drawn to non-elected subject matter, the previous restriction requirement have been made final.

Claims 1 and 17 have been amended to delete the term "C<sub>1-6</sub>alkyl" from the definition of R<sup>4</sup> and to add the term "nitro" to list of possible substituents for aryl and heteroaryl. This latter amendment is supported by the specification at page 20, the compound of formula I(o), and by claims 10 and 18 as originally filed.

Claim 5 has been amended to replace the term "toclaim" with "to claim" as requested by the Examiner. This amendment corrects an obvious typographical error and in no way alters the scope of the claim.

Claims 1, 12, 13 and 16 have been amended to correct an obvious typographical error in the spelling of the term "cycloalkyl." These amendments are of a clerical nature and do not alter the scope of these claims in any way.

Claim 10 has been amended to correct an obvious typographical error in the spelling of the terms "dichlorophenyl," "trifluoromethylphenyl" and "nitrophenyl." These amendments are of a clerical nature and do not alter the scope of this claim in any way.

Claim 11 has been amended to correct an obvious typographical error in the spelling of the term "dichlorophenyl." This amendment is of a clerical nature and does not alter the scope of this claim in any way.

Claim 16 has been amended to add the term "nitro" to list of possible substituents for aryl and heteroaryl. This latter amendment is supported by the specification at page 20, the compound of formula I(o), and by claims 10 and 18 as originally filed.

Claim 18 has been amended to remove compounds I(v), I(w), I(x), I(y) and I(gg) to maintain consistency with the amendments made to claim 1.

Claims 19 and 20 have been amended to change their dependency from claim 1 to claim 18. This represents a clarifying amendment.

Applicants have made the claim amendments without prejudice and without acquiescing to any of the objections mentioned in the Office Action. The Applicants reserve the right to file any

canceled subject matter in one or more divisional patent applications. The Applicants submit that no new matter has been entered by the present amendment and respectfully request their entry.

The Official Action dated October 25, 2005 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response. Reconsideration is respectfully requested.

#### Claim Objections

#### **35 U.S.C. §112, Second Paragraph**

The Office has rejected claims 19 and 20 under 35 U.S.C. §112, second paragraph, as indefinite on the ground that there is insufficient antecedent basis for the terms "I(a), I(e) ...". Claims 19 and 20 have been amended to change their dependency from claim 1 to claim 18. Claim 18 provides proper antecedent basis for each of the compounds claimed in claims 19 and 20. Accordingly the Examiner's rejection has been overcome.

In view of the above amendments the Applicants submit that the claims comply with the standards of 35 U.S.C. §112, second paragraph, and therefore request that the rejection of claims 19 and 20 be withdrawn.

The Examiner has objected to claims 10 and 18 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically the Examiner notes that R<sup>4</sup> in claim 10 and 18 may be 4-nitrophenyl, which is not encompassed by the definition of R<sup>4</sup> in claim 1. Claim 1 has been amended to add the term "nitro" to the list of possible substituents on the aryl and heteroaryl groups in the definition of R<sup>4</sup>. This amendment is supported in the specification at page 20 by formula I(o) and by claims 10 and 18 as originally filed. The compound of formula I(o) in the specification and in claim 18 includes a nitrophenyl group at R<sup>4</sup>. Claim 10 as originally filed includes "4-nitrophenyl" in the list of definitions for R<sup>4</sup>.

Applicants submit that the claims are of proper dependent form. Therefore, in light of the above amendments, the Examiner is requested to withdraw the objection to claims 10 and 18 under 35 U.S.C. §112, second paragraph.

**35 U.S.C. §102(b)**

The Examiner has rejected claims 1-4, 12-14, 17 and 23 under 35 USC §102(b) as anticipated by Posner et al. (J. Med. Chem., 1999). The Examiner submits that Posner et al. teaches sulfone analogues of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, in particular compound 3a, that are encompassed by the instant claims.

By the present amendment, claims 1 and 17 have been amended to remove the term "C<sub>(1-6)</sub>alkyl" from the definition of R<sup>4</sup>. The remaining claims (2-4, 12-14 and 23) depend from either claim 1 or claim 17. The Applicants submit that Posner et al. does not teach or suggest compounds of formula I where the group R<sup>4</sup> is unsubstituted or substituted aryl or heteroaryl therefore the Examiner's rejection has been overcome.

In view of the amendments described above the Examiner is requested to withdraw the rejection of claims 1-4, 12-14, 17 and 23 under 35 U.S.C. §102(b).

**35 U.S.C. §103(a)**

The Examiner has rejected claims 1-10, 12-20 and 23 under 35 U.S.C. 103(a), as obvious over DeLuca et al. (US 4,927,815). The Examiner specifically points to column 4, lines 45-63 of DeLuca which describes an intermediate structure useful in the preparation of vitamin D derivatives having biological properties. The Applicants respectfully traverse this rejection.

The Office Action states:

[I]t would have been obvious to one having ordinary skill in the art at the time of the present invention to select any of the species of the genus taught by the reference, including that of the instant claims, because he would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, would be

useful in the preparation of biologically active vitamin D derivatives as taught by the reference.

Courts have stated, however, that:

[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification.

*In re Lintner*, 173 U.S.P.Q. 560, 562 (C.C.P.A. 1972). Further, a *prima facie* case of obviousness is established only when "teaching from the prior art itself would appear to have suggested the *claimed subject matter* to a person of ordinary skill in the art." *In re Rinehart*, 189 U.S.P.Q. 143, 147 (C.C.P.A. 1976) (emphasis added). Therefore, the Examiner must show the subject matter of claims 1-10, 12-20 and 23 is suggested by the combination of DeLuca and the knowledge of a person skilled in the art.

An initial question is whether the cited prior art is analogous to the art of the invention and whether the problem solved therein is related to or is applicable to the problem solved by the present invention. A person skilled in the art, upon reading DeLuca, would see that it shares in common with the present invention, a solution to the problem of finding new vitamin D analogs. This problem is summarized in DeLuca as follows:

The present invention provides a novel class of compounds exhibiting a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by a high potency (compared to that of 1,25-(OH)<sub>2</sub>D<sub>3</sub>) inducing the differentiation of malignant cells, while exhibiting much lower

activity than 1,25-(OH)<sub>2</sub>D<sub>3</sub> in their effect on calcium metabolism.

U.S. Patent No. 4,927,815, column 2, lines 44-50.

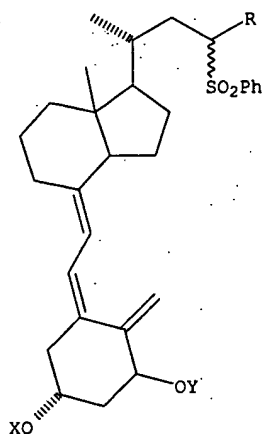
However, the solution to this problem provided by DeLuca is *completely different* to that provided by the present invention. At column 2, line 62-66, the DeLuca patent identifies the key structural feature of the active compounds therein:

"[s]tructurally, the key feature of the compounds having these desirable biological attributes is that they are side chain homologs of 1,25-(OH)<sub>2</sub>D<sub>3</sub> in which the side chain is elongated by insertion of two or three methylene units into the chain." The compounds of the present application do *not* contain the key structural feature described by DeLuca to be required for biological activity. Accordingly, a person skilled in the art would not have been led by the teachings in DeLuca to the compounds of the present application for use in solving the problem of providing derivatives of 1,25-(OH)<sub>2</sub>D<sub>3</sub> with improved biological profiles.

The Office indicates in the Action that the problem solved by DeLuca is providing compounds that would be useful in the preparation of vitamin D derivatives. If this is indeed the case, then the problem solved by DeLuca is wholly different from that solved by the present invention. The present invention does not relate to compounds that are useful as intermediates in the preparation of vitamin D derivatives. In no place in the disclosure of the present application is it taught, or even suggested, that the compounds of Formula I of the present invention could be used as intermediates in the preparation of

other vitamin D derivatives, nor is it even mentioned that it would be desirable to do so.

DeLuca describes at column 4, lines 45-63, a structure containing a phenyl-sulfone compound as shown below:



where R is alkyl, hydroxy-substituted alkyl and fluoro-substituted alkyl and where the hydroxy groups may be derivatized by hydroxy protecting groups. DeLuca proposes this type of compound only as an intermediate used in the preparation of the active compounds having the extended side chain as described above. DeLuca does not attribute any special significance to these sulfone compounds nor does he attribute any usefulness to these compounds aside from their use as intermediates for the preparation of other vitamin D derivatives. It should be noted that the only vitamin D derivatives prepared by DeLuca containing a sulfone moiety in the side chain are compounds 29 and 30 shown in Process Scheme 4. These compounds contains the "key structural feature" (column 2, lines 61-65) of an insertion of extra methylene units into the side chain and thus is vastly different from the compounds of the present invention.



The rejection is based on improper conclusions and improper hindsight evaluation of the prior art. The problem solved by DeLuca, at least with respect to vitamin D derivatives containing a sulfone in the D-ring side chain, is *completely different* from that in the present invention. In other words, a person skilled in the art would *not* have looked to DeLuca to provide solutions to the problem solved by the present invention, that is, new vitamin D derivatives with improved biological activity having a aryl or heteroaryl sulfone moiety in the D-ring side chain. Further, there is no suggestion in DeLuca that such compounds should be used or would have the desired activity since DeLuca teaches only to extend the side chain with methylene groups and not to create the aryl and heteroaryl groups of these claims.

The Federal Circuit has repeatedly warned that the requisite motivation to modify the prior art to arrive at an Applicant's invention must come from the prior art, not Applicant's specification. It is, therefore, improper to "[use] that which the inventor taught against its teacher." *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002) (citing *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir 1983)). This is improper use of hindsight since it relies on knowledge concerning aryl groups and their effect which was not taught or suggested in the DeLuca reference. See M.P.E.P. § 2145.

"[T]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure." *In re Dow Chem. Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). And "[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the

modification." *In re Laskowski*, 10 USPQ 2d 1397, 1398 (Fed. Cir. 1989) (quoting *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984)).

Applicants also would like to point out that although DeLuca taught a potent activity for the compounds having the key feature of methylene-elongated chains, the reference does not attribute this function to the compounds claimed here. Furthermore, the sulfone compositions used by DeLuca were taught only to be intermediates. If the prior art does not teach any specific or significant utility for disclosed compounds, for example teaching use as an intermediate only, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill to make the prior art compounds, much less any structurally similar compounds. Applicants refer the Office to M.P.E.P., Rev. 3, August 2005, § 2144.09, page 2100-165, which explains this point of practice.

Applicants submit that the art cited is not sufficient to make out a *prima facie* case of obviousness against the claims presented here and is entirely inadequate to provide a suggestion to modify the art to achieve the present invention. Therefore, the Office has not met its burden to find motivation to modify the prior art reference and thereby render the present invention obvious. Not only was the problem solved by the present invention not known, but there is no suggestion to modify DeLuca to solve the problem of the present invention.


In light of the arguments provided above, the Applicants request that the rejection of claims 1-10, 12-14, 17 and 23 under 35 U.S.C. §103(a) be withdrawn.

**Other Matters**

The Office has noted that a space is missing between the words "to" and "claim 1" in claim 5. As requested, claim 5 has been amended to add a space between the words "to" and "claim 1." In view of this amendment, the Examiner is requested to withdraw the objection to claim 5.

The Applicants request that claims 1-20 and 23 be allowed at this time. Further, since claims 1-20 and 23 and claims 24-35, 46-52 and 60-64 are related as product and process and the process claims include all of the elements of the product claims, Applicants also request that process claims 24-35, 46-52 and 60-64 be rejoined with product claims 1-20 and 23 as permitted by MPEP §821.04 and discussed in the Office Action dated August 5, 2005.

In view of the foregoing comments and amendments, we respectfully request reconsideration of application and of the claims as amended. If any issues remain in the view of the Office, the Examiner is invited to contact the undersigned by telephone at the Examiner's convenience.

<b>RESPECTFULLY SUBMITTED,</b>					
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